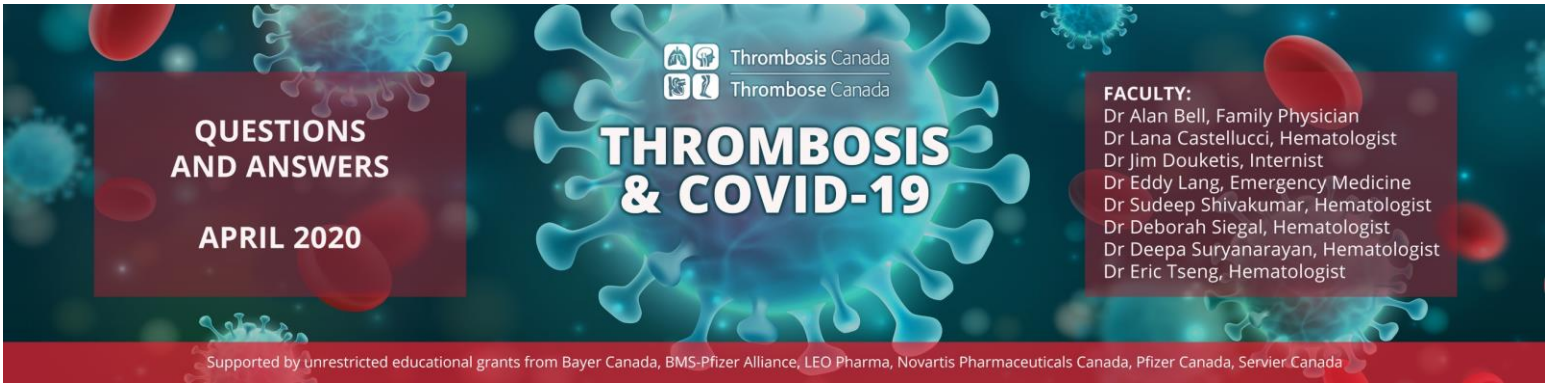

D-dimer

1. **How do you address anticoagulation for isolated significantly elevated dimer in a COVID-ARDS critically ill patient, especially if D-dimer increases rapidly and markedly (e.g., 2,000 to >10,000)?**

   Many patients admitted to hospital/ICU with COVID-19 have elevated D-dimer levels. Elevated D-dimer levels alone are not diagnostic of venous thrombosis and are not an indication to investigate for VTE in the absence of clinical findings. For rapid changes in D-dimer levels, other causes should be assessed including renal failure and secondary infection. Therapeutic anticoagulation is recommended for imaging confirmed DVT and PE, but it is not recommended empirically based on changes in D-dimer levels alone. All admitted patients are recommended to received DVT prophylaxis.

2. **Should an elevated D-dimer prompt diagnostic testing for PE?**

   Many patients admitted to hospital/ICU with COVID-19 have elevated D-dimer levels. Elevated D-dimer levels alone are not diagnostic of venous thrombosis and are not an indication to investigate for VTE in the absence of clinical findings. For rapid changes in D-dimer levels, other causes should be assessed including renal failure and secondary infection.

3. **Should an elevated D-dimer prompt adjustment of the thromboprophylaxis dose?**

   An elevated D-dimer is common in hospitalized medical patients including those with COVID-19. All patients with COVID-19 should receive at least standard-dose thromboprophylaxis with LMWH (UFH in the setting of end-stage renal disease), irrespective of D-dimer level. There is no established correlation between D-dimer level and risk for VTE and the dose of thromboprophylaxis should be adjusted according to patient weight and other VTE risk factors.

Diagnosis of PE

4. **What is the optimal diagnostic test for PE in patients with suspected or confirmed COVID-19?**

   In general, the preferred diagnostic test is CT pulmonary angiography (CTPA), as it able to distinguish PE in the setting of concurrent interstitial or alveolar disease related to COVID-19 better than

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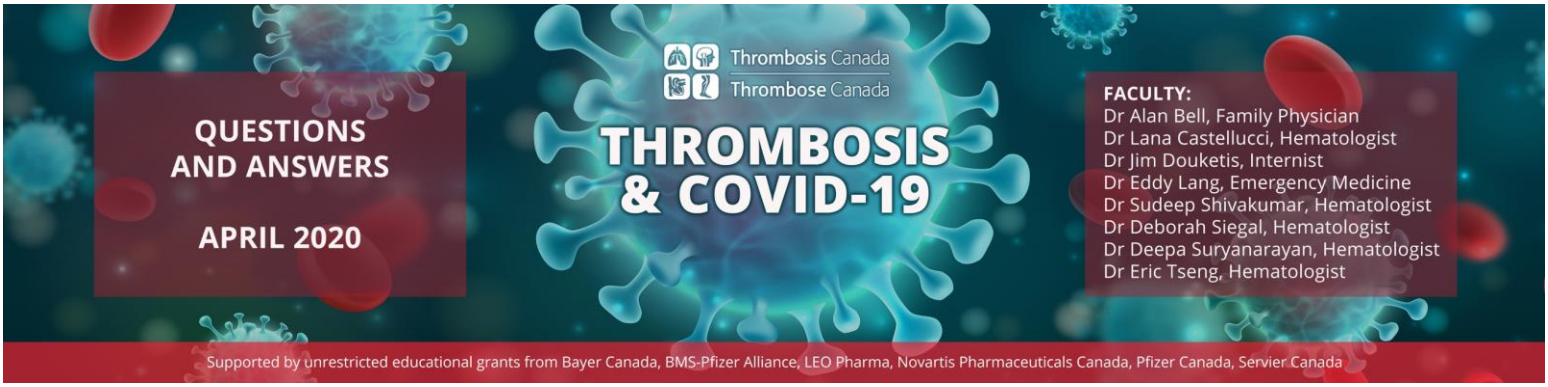

ventilation-perfusion scanning. CTPA is easier to perform in critically ill patients although may be challenging in patients with severe renal insufficiency or allergy to IV contrast dye.

5. **How do you diagnose PE in patients who are too unstable or for whom imaging not feasible (e.g. very obese)?**

   Some patients may be too unwell to safely transfer for investigations of PE. In these cases, bilateral doppler ultrasound of lower extremities is recommended to evaluate for presence of DVT. If DVT is present, therapeutic anticoagulation should be started, provided there is no contraindication to anticoagulation.

   In patients that are too unstable to undergo dedicated imaging for possible PE and have no evidence of DVT on ultrasound imaging, bedside echocardiogram may be performed to evaluate for signs of right ventricular dysfunction, and rarely, clot in transit. If patients are in prone position for severe hypoxia, it is unlikely that any investigation and documentation of VTE will change outcomes. There is little data to support use/initiation of empiric therapeutic anticoagulation in the absence of confirmed PE diagnosis. The risk of major bleeding in severely ill patients with risk factors for bleeding such as liver and renal dysfunction must also be considered.

   The American Society of Hematology considers that, in cases where there is no possibility of performing imaging to diagnose VTE and no contraindication to therapeutic anticoagulation, empiric anticoagulation may be considered for:

   - Intubated patients with sudden change in clinical and lab findings consistent with PE, and chest x-ray findings or other inflammatory markers are stable;
   - Patients with physical exam findings of VTE including superficial thrombosis, peripheral ischemia/cyanosis, clotting of catheters/tubing/dialysis circuits;
   - Patients with respiratory failure, very high D-dimer and fibrinogen levels, and high suspicion of PE or microvascular thrombosis and no other cause identified (e.g. fluid overload).

DVT Prophylaxis

6. **What VTE prophylaxis regimens are currently recommended for COVID+ inpatients in ICU and non-ICU settings?**

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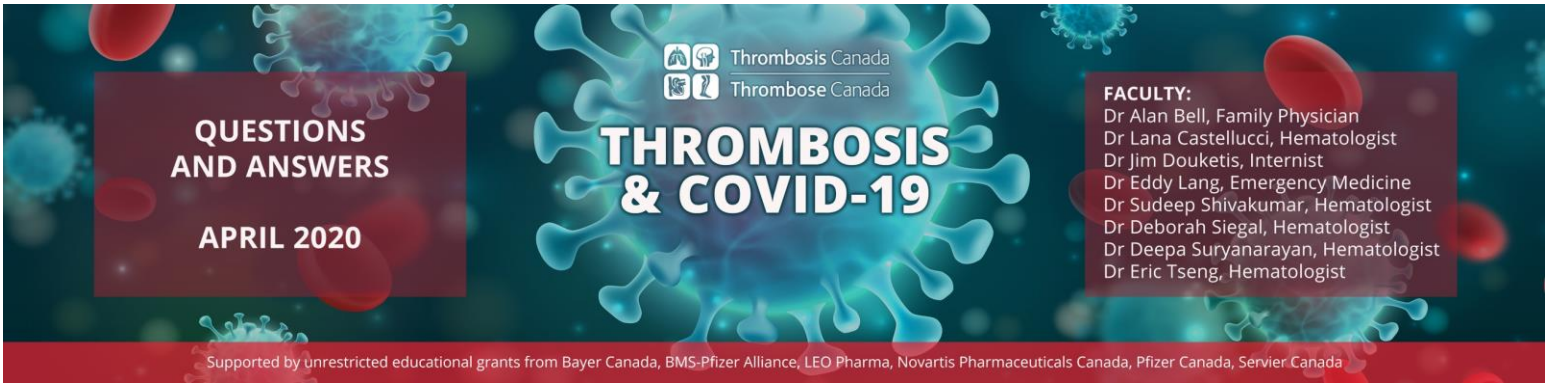

All patients admitted to hospital with COVID-19 infection should receive standard prophylaxis doses of LMWH or subcutaneous UFH. The prophylaxis dose may be adjusted for weight in patients with increased body mass index. Typically, this would involve increasing the LMWH dose by 50%.

As regards the dose of thromboprophylaxis, some observational studies have demonstrated high VTE rates in patients with COVID-19 admitted to ICU, despite the use of standard dose VTE prophylaxis. However, there is currently no high-quality evidence that supports the empiric use of intermediate or therapeutic doses for VTE prophylaxis in the ICU setting. Therefore, while some centres have recommended using intermediate doses in critically ill patients, typically 1.5- to 2-fold higher than the standard LMWH dose, it is currently recommended that ICU and non-ICU inpatients receive standard weight-adjusted thromboprophylaxis. Other empiric regimens can be considered within the context of a clinical trial.

7. Should VTE prophylaxis doses be empirically adjusted according to different D-dimer levels?

Marked, persistent elevations in D-dimer have been associated with mortality in patients admitted with severe COVID-19 infection. Early data from Wuhan have suggested that heparin prophylaxis may provide a mortality benefit in a subset of patients with markedly high D-dimer, but these data were observational and did not adjust for potential confounders.

It remains unclear whether high D-dimers in COVID-19 reflect hypercoagulability and thrombosis, or merely the underlying proinflammatory state. There is also no high-quality evidence in COVID+ (or even non-COVID) inpatients that adjusting VTE prophylaxis dosing based on D-dimer level is efficacious or safe. Therefore, it is currently recommended that standard VTE prophylaxis doses be used in patients with high D-dimers without established VTE, except in the clinical trial setting.

Of note, in patients with high D-dimer levels and suspicion of VTE (based on clinical status or physical examination findings), efforts should be made to objectively diagnose VTE (leg dopplers, echocardiogram, POCUS, CTPA or V/Q scan if possible) before providing empiric therapeutic anticoagulation for presumed VTE.

8. How long should COVID+ inpatients receive VTE prophylaxis for?

In most cases, patients admitted to hospital should receive daily thromboprophylaxis for the duration of their admission. There is no clear evidence for the use of extended, post-discharge prophylaxis after COVID infection and as such, its use is not routinely recommended. However,

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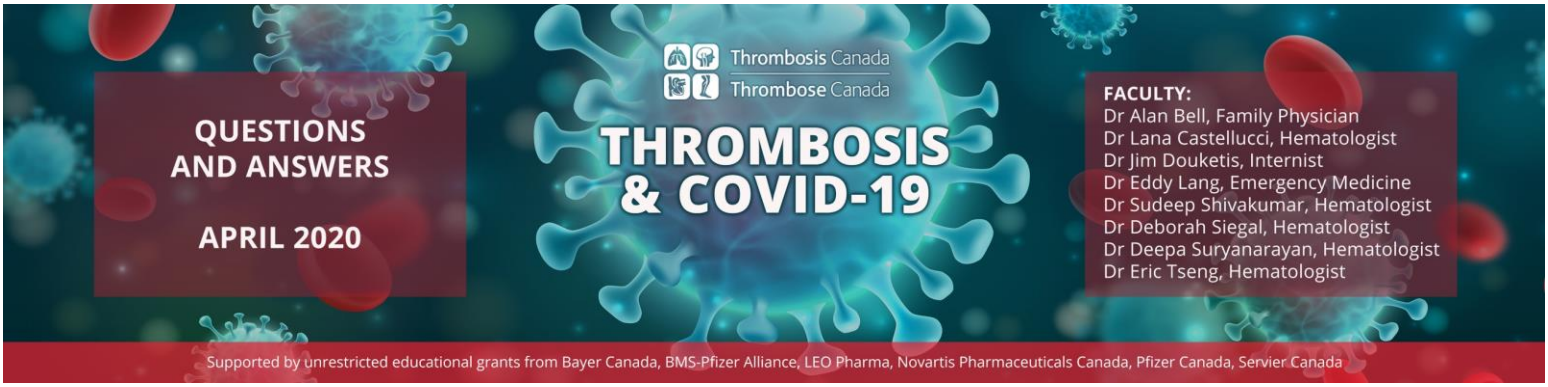

evidence from (non-COVID) randomized studies has suggested that there may be net benefit for providing post-discharge prophylaxis in selected high-risk medical inpatients. Therefore, in COVID patients being discharged it may reasonable to consider post-discharge prophylaxis on a case-by-case basis taking into account thrombotic risk factors (such as active cancer, previous VTE history, reduced mobility) along with assessing bleeding risk.

9. What anticoagulation regimens are suggested for patients who are on Extracorporeal Membranous Oxygenation (ECMO)?

There is currently a paucity of published data on optimal anticoagulation regimens in patients on ECMO. It is recommended that providers follow their typical institutional anticoagulation regimen in these patients, with hematology consultation as indicated.

10. Are there any clinical trials comparing different doses (prophylactic, intermediate, therapeutic) of anticoagulation for VTE prophylaxis in COVID+ patients?

There are several such clinical trials being planned. One (COVID-HEP) is currently listed in ClinicalTrials.gov (NCT04345848) in COVID+ patients admitted to ICU or non-ICU settings comparing therapeutic versus prophylactic dose enoxaparin, with the primary composite outcome of arterial or venous thrombosis, disseminated intravascular coagulation, and all-cause mortality at thirty days. In the coming weeks it is likely that additional trials comparing different intensities of prophylactic anticoagulation will begin, including Canadian sites. This section will be updated as more information becomes available.

11. What is the role of primary VTE prophylaxis (with anticoagulants or aspirin) for outpatients who are in the ambulatory or long-term care setting?

There are no high-quality studies examining the prevalence of VTE in COVID+ outpatients, particularly as most infected patients do not develop severe disease requiring hospitalization. As such these outpatients should not routinely receive primary thromboprophylaxis in the absence of another indication.

Patients residing in LTC facilities, in general, may be at higher baseline thrombotic risk due to chronic medical conditions and reduced mobility. It is unknown whether COVID19 infection increases the risk of VTE in these patients who reside in LTC who are nevertheless well enough that

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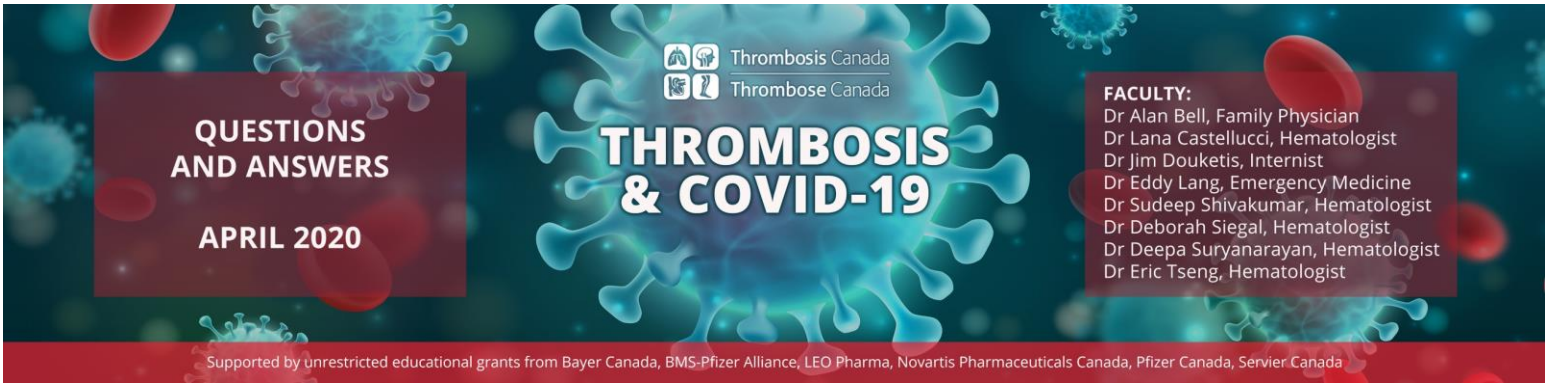

they do not require hospital admission. Furthermore, such LTC residents may have other bleeding risk factors or be on other antithrombotic therapies already. It is not currently recommended that such patients routinely receive pharmacologic prophylaxis except perhaps in high-risk circumstances with multiple thrombotic risk factors and severe mobility restriction.

12. In patients who were receiving chronic anticoagulant therapy, either a DOAC or warfarin, and require ICU management, should their anticoagulant be switched to LWMH or UFH?

In general, it is advisable to consider interrupting oral anticoagulants (DOAC, warfarin) upon admission to an ICU/CCU and replacing them with a parenteral anticoagulant, preferably therapeutic-dose LMWH. The rationale for this is that LMWHs are easier to administer than warfarin (no need for INR testing), do not have drug interactions with potential COVID-19 treatments (DOACs may have drug interactions) and undertaking procedures and interventions are easier (LMWHs have short half-lives).

Coagulopathy and laboratory-related questions

13. What is the prognostic importance of elevated D-dimer, and the need for serial D-dimer measurement?

D-dimer is a breakdown product of cross-linked fibrin which is elevated in the setting of acute thrombosis, but also inflammation, cancer, and infections. For example, D-dimer levels are known to be elevated in critically ill patients without COVID-19. Although severe COVID-19 is associated with high D-dimer levels, the precise relationship between D-dimer and outcomes is uncertain. Available data suggest that increased D-dimer levels in hospitalized patients with COVID-19 are associated with higher risks of thrombosis, mechanical ventilation, transfer to intensive care unit and death. As our understanding about the nature of the coagulation abnormalities in COVID-19 and their relationship to thrombosis evolves, it is reasonable to measure D-dimer, PT, aPTT and fibrinogen levels in hospitalized patients with COVID-19. INR testing may not be sufficiently sensitive to detect coagulopathy. Because we have insufficient evidence to make treatment recommendations based on D-dimer levels, the role for serial testing is uncertain. However, serial testing may help monitor the clinical course in individual patients, characterize the coagulopathy present and conduct research to further understand the clinical implications of these findings.

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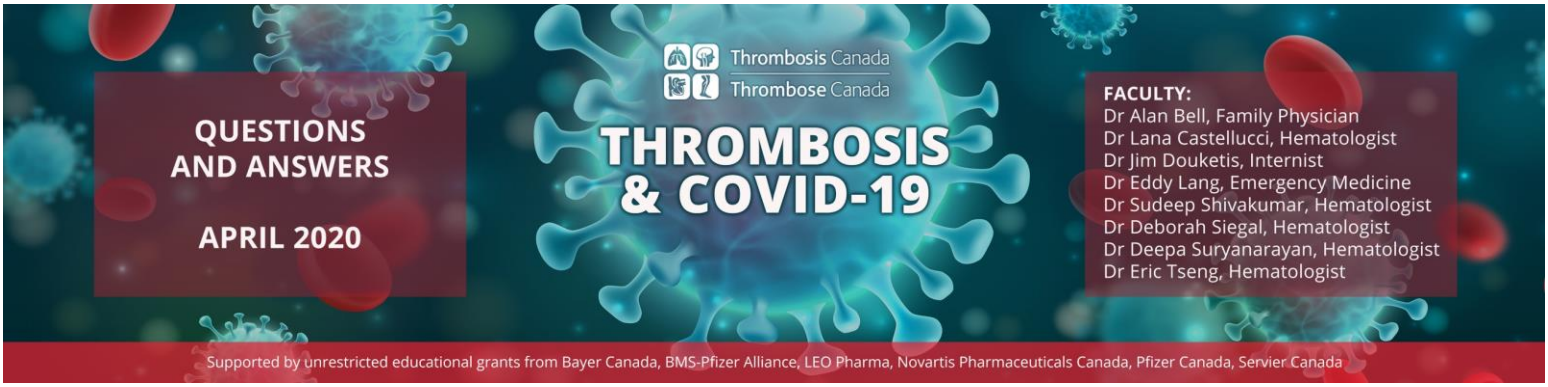

14. What is the relevance of DIC score and how does it impact the need to administer/adjust anticoagulant intensity?

Disseminated intravascular coagulation (DIC) is characterized by activation of coagulation and fibrinolysis and is a complication of underlying sepsis, malignancy, trauma, and obstetrical complications (among others). Activation of coagulation results in the production of thrombi resulting in consumption of coagulation factors, platelets and natural anticoagulants (e.g. protein C, protein C, antithrombin). Fibrinolysis at the sites of thrombosis generates fibrin degradation products (e.g. D-dimer). The ISTH DIC score was developed and validated in non-COVID-19 patients with DIC. The score includes platelet count, fibrin related marker (e.g. D-dimer), prothrombin time (PT) and fibrinogen levels and higher points are assigned for higher degrees of thrombocytopenia, elevation of fibrin marker and hypofibrinogenemia. Higher scores have been shown to correlate with higher mortality in non-COVID-19 patients. However, the coagulopathy associated with severe COVID-19 appears to have some important differences such as normal or elevated fibrinogen and lower degrees of thrombocytopenia and, therefore, the validity of the ISTH DIC score for predicting outcomes in COVID-19 patients is uncertain. At this point, there are insufficient data to recommend treatment modifications based on DIC score.

15. What is the effect of COVID-19 on INR/PT and other coagulation parameters?

Coagulation abnormalities reported in severe COVID-19 include mild thrombocytopenia, prolonged PT, prolonged aPTT and elevated INR, although the latter is considered less sensitive than PT for coagulopathy in this setting. In contrast with hypofibrinogenemia associated with coagulopathy/DIC in non-COVID patients with sepsis, fibrinogen levels in patients with severe COVID-19 are more frequently normal or elevated.

16. What is the clinical utility (if any) of TEG or ROTEM to assess hypercoagulability in COVID patients?

A small case series of COVID-19 patients admitted to the intensive care unit showed TEG indices consistent with hypercoagulability. At this time there are insufficient data to inform the clinical utility of TEG, ROTEM and thrombin generation assays in patients with COVID-19.

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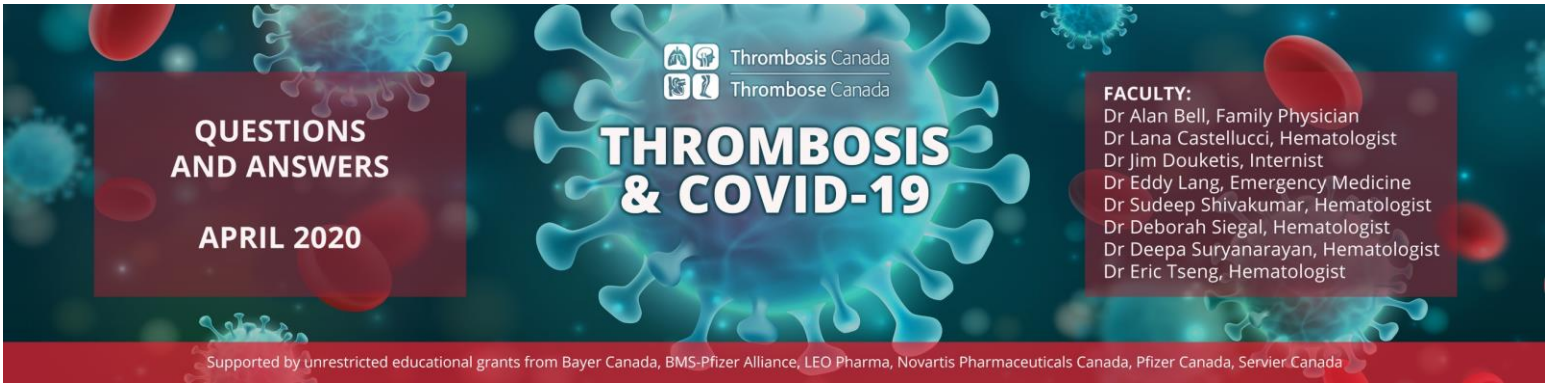

17. What is the clinical significance of elevated inflammatory markers (ferritin, CRP)?

Severe COVID-19 is associated with a profile of elevated inflammatory cytokines such as IL-6 reminiscent of cytokine release syndrome (CRS)-induced ARDS and secondary hemophagocytic lymphohistiocytosis (sHLH). The terms “cytokine storm” and “hyperinflammation” have also been used to describe these findings in COVID-19. Elevated serum IL-6 levels correlate with respiratory failure, ARDS and other adverse clinical outcomes. The expression of CRP is driven by IL-6 and it is elevated in COVID-19. Ferritin is an acute phase reactant and hyperferritinemia is also found in COVID-19. There are insufficient data at this to make specific recommendations regarding the treatment of COVID-19 associated hyperinflammation. Such patients should be considered for clinical trials evaluating immune modulating therapies. Guidance from the WHO and other infectious diseases authorities caution against the use of corticosteroids in COVID-19 at present.

18. What is the relation between complement, vWF, blood type, ADAMTS-13 and thrombosis, if any?

Limited data suggest that von Willebrand factor (vWF) activity and antigen are increased in patients with severe COVID-10. Preclinical data from mouse models suggest that complement activation occurs with SARS-CoV-2 (the virus that causes COVID-19). There are currently no peer-reviewed published studies that have evaluated a relationship between ABO (or other) blood group and susceptibility to COVID-19.

Therapy-related questions

19. I heard that there is a need to avoid IV heparin as there is a high risk that polysaccharide molecule may carry the virus and displace heparin from its binding site, and this has the potential to cause paradoxical thromboembolism. Is this true?

There is no scientific evidence to support this premise and intravenous heparin should be used when clinically indicated in COVID-19 positive patients.

20. What is the anticoagulant management for cerebral infarctions in seriously ill patients with coagulopathy/overt DIC with and without thrombocytopenia?

In general, therapeutic-dose anticoagulation should be avoided in patients with ischemic stroke and such patients should receive low-dose LMWH for prophylaxis against VTE. In patients with stroke

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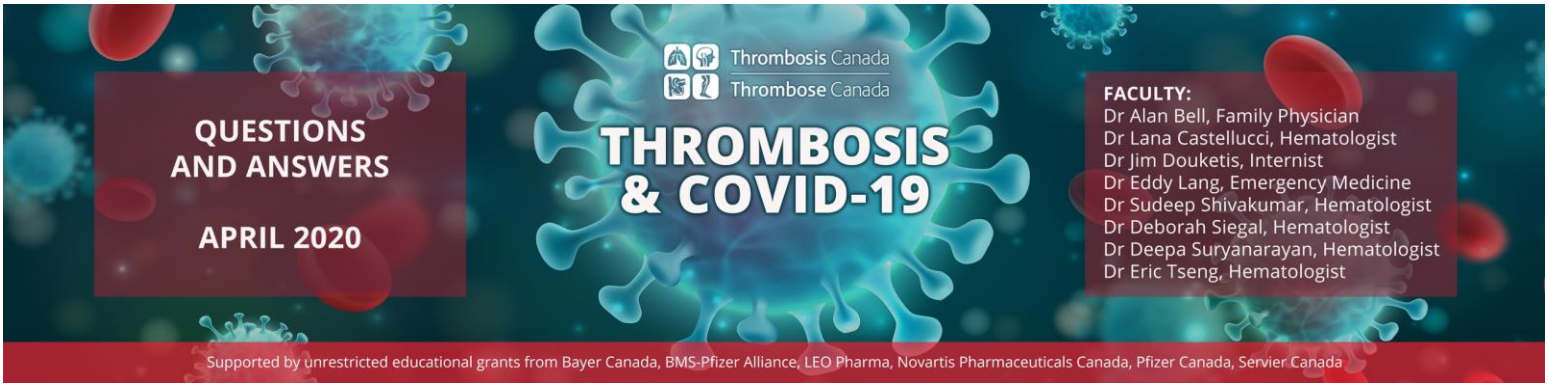

and DIC, management should be individualized to reflect whether the DIC has a prohemorrhagic or prothrombotic tendency, preferably in consultation with a hematologist and stroke neurologist.

21. Should I be concerned about pulmonary hemorrhage with anticoagulant management?

To date, there is no scientific evidence that COVID-19 positive patients are at increased risk for intrapulmonary hemorrhage and intravenous heparin should be used where appropriate.

22. What is the role of low-dose (tPA, 1 mg/hr) systemic lytic therapy for severe ARDS?

There is no scientific evidence for benefit with the use of low-dose tPA in COVID-19 positive patients with an ARDS clinical picture, and potential for bleeding complications.

23. What is the INR monitoring frequency with/without POC devices?

In patients who are receiving warfarin and have good INR control, INR testing can be safely spread out so that it is done every 8-12 weeks. This can also be applied to patients who self-monitor with POC devices. In general, consideration should be given to transitioning patients from warfarin to a DOAC, where clinically appropriate, to simplify anticoagulant management and to minimize encounters with health care professionals.

24. How do we manage INRs >5 or >10?

In most cases, the management of patients with an elevated INR can be done without the need for an in-person encounter. The vast majority of cases of elevated INRs >5 occur in asymptomatic patients and can be dealt with by withholding warfarin for 1-2 days and giving oral vitamin K (1-2 mg) for an INR >10. In patients with minor bleeding (epistaxis, hemorrhoidal bleeding, soft tissue bruising) the same approach as above can be used.

25. What is the choice of parenteral anticoagulant for hospitalized patient: IV UFH vs. SC LMWH vs. DOAC?

The choice of anticoagulant used will depend on the clinical indication and patient-specific consideration. In general, it is advisable to select either a once-daily administered LMWH or a DOAC

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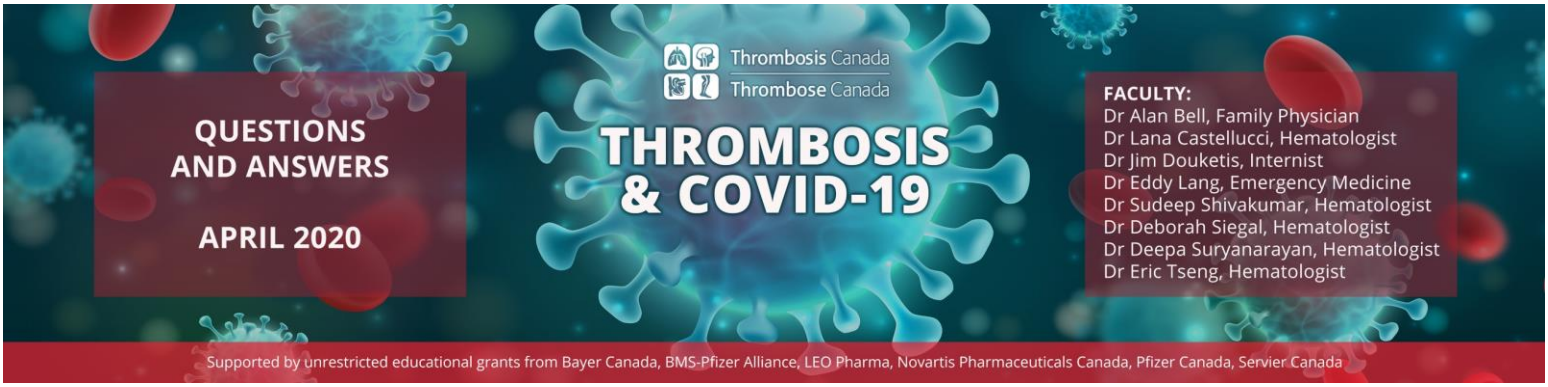

to limit patient interactions and blood draws and to facilitate transition to anticoagulation after discharge from hospital.

Special Populations

26. Does COVID-19 increase circuit clotting in patients on dialysis or SLEDD? How is this best managed?

Coagulopathy is being widely recognized as a complication with severe COVID illness and there are anecdotal reports of excessive clotting with the CRRT circuit in patients requiring dialysis or SLEDD. There are currently limited published data on the appropriate anticoagulation dosing regimens specifically in this patient population and hence recommend following your institutional guidelines with hematology consultation when needed to make decisions regarding systemic anticoagulation. In case of frequent line clotting it is still imperative to exclude other pro-thrombotic conditions such as HITT/APLA. Alternative strategies cited in anecdotal reports have included using citrate and heparin or argatroban but evidence in COVID patients is lacking. Non anticoagulant strategies remain key in prolonging filter survival as per existing guidelines (Kellum JZ, et al. KDIGO clinical practice guideline for acute kidney injury. 2012)

LMWH are renally cleared and hence bio accumulation can occur in impaired renal function. There is an inverse relationship between CrCl and anti-Xa levels, but this varies amongst different LMWHs. LMWHs with larger oligosaccharide chains such as dalteparin or tinzaparin have been shown to be less dependent on renal function than LMWHs with lower molecular weight such as enoxaparin or nadroparin. Anti-Xa monitoring and or dose reduction should be considered if enoxaparin or nadroparin are used in patients with a CrCl of <30 mL/min to ensure there is no accumulation. Available evidence for tinzaparin has demonstrated no accumulation in patients with CrCl level as low as 20 mL/min but data is limited in patients with CrCl<20 mL/min. If rapid anti-Xa levels are unavailable or difficult to obtain based on current limited trial evidence use higher molecular weight LMWH with extreme caution and close clinical monitoring or ideally switch to UFH where possible.

27. What is the evidence on COVID in pediatric patients?

Data in pediatric patients regarding VTE is scant. A series of 2135 pediatric patients with suspected or confirmed COVID from China (Dong Y, et al. Pediatrics, 2020) found a median age of 7 years, but children of all ages were susceptible. Over 90% of pediatric patients were asymptomatic or were mild/moderate cases, and median onset from illness onset to diagnosis was 2 days (range 0-42

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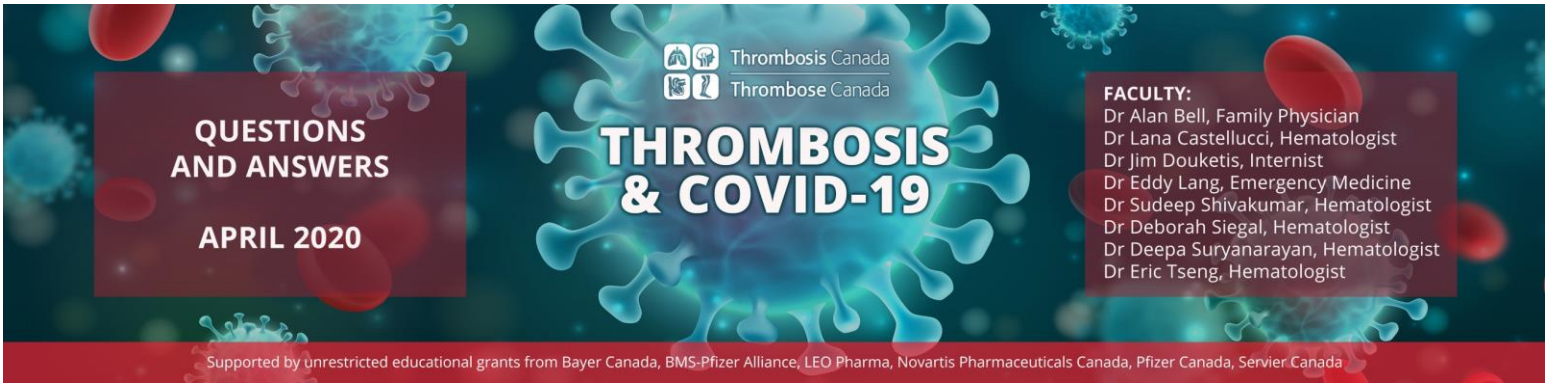

days). Incidence of VTE was not reported. An observational cohort study from Zhejiang, China included 36 confirmed pediatric cases and also found that the majority of cases were asymptomatic, mild or moderate, and a high d-dimer was found to be significantly associated with severe cases; again, VTE was not reported. VTE prophylaxis for pediatric inpatients should be discussed with Pediatrics at individual sites, but is not explicitly mentioned in recent guidelines by the Canadian Pediatric Society.

28. Are ACE-Is and ARBs safe in COVID-19 patients?

Our colleagues at Hypertension Canada have provided the following guidance:

Based on evidence available as of the date of this release:

- *A high proportion of patients hospitalized with COVID-19 have high blood pressure (hypertension).*
- *However, there is no evidence that patients with hypertension or those treated with ARB or ACE inhibitor antihypertensive therapy are at higher risk of adverse outcomes from COVID19 infection.*
- *We endorse patients with hypertension to continue with their current blood pressure treatment.*

29. What is the recommendation for VTE prophylaxis in patients with mental health problems/restraints?

There is no specific evidence in this population, and they would be presumed to have a similar risk of VTE as the general population with COVID-19. Thus, we would recommend prophylactic dosing of LMWH for any inpatient to a COVID ward, with weight-based modifications as necessary. Special considerations in this population include drug-drug interactions, which would favor the use of LMWH over DOACs, and needle phobias, which may make the administration of LMWH difficult, but still preferred over other anticoagulation choices if at all possible.

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